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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,782	07/09/2001	Susan Hardin	IVGN 1013	9388
7590 Todd R. Walters, Esq. BUCHANAN INGERSOLL & ROONEY PC 1737 King Street, Suite 500 Alexandria, VA 22314			EXAMINER SISSON, BRADLEY L	
			ART UNIT	PAPER NUMBER
			1634	
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			02/23/2010 PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

09/901,782

**Applicant(s)**

HARDIN ET AL.

**Examiner**

Bradley L. Sisson

**Art Unit**

1634

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 10, 16-19, 50-56, 64-74, 76-92, 94-106 and 108-111 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 10, 16-19, 50-56, 64-74, 76-92, 94-106 and 108-111 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 10 March 2009.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10 March 2009 has been entered.
2. It is noted that the response of 10 March 2009 did not contain any amendment to the specification and/or claims and that no rebuttal of the prior rejections has been made. Accordingly, the prior final Office action is effectively repeated herein below.

### ***Specification***

3. The specification remains objected to as documents have been improperly incorporated by reference. It is noted that the specification contains reference to numerous documents, yet the complete bibliographical citation has not been provided. In general, only the last name of the first named author and publication year are provided. A review of the original specification fails to find where any bibliographical index has been provided. As a consequence, it is not readily apparent as to just which journal(s) the publications appeared in, much less identify where in the various articles the essential materials is to be found. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6<sup>th</sup> Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application). (Emphasis added.)

4. Accordingly, the cited documents are not considered to have been incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.

#### ***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10, 16-19, 50-56, 64-74, 76-92, 94-100, 102-106 and 108-111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Currently claims 10, 50, 64, 71, 79, and 89 are the only independent claims pending. Each of said claims has been found to contain the expression “undergoes a change before, during, and/or after.” It is unclear, and possibly impossible, for something to be undergoing a “change” before, during, and after, as such an embodiment encompasses all possible time periods. Claims 16-19, 51-56, 65-70, 72-74, 76-78, 80-88, 90-92, 94-100, 102-106, and 108-111, which depend from said independent claims, fail to overcome this issue and are similarly rejected.

8. Claims 19, 56, 70, 78, 88, and 99 are indefinite as they all provide a range of numbers, which are without value and without reference point.

9. Assuming *arguendo*, that the numbers presented in claims 19, 56, 70, 78, 88, and 99 are in reference of amino acid positions, said claims 19, 56, 70, 78, 88, and 99 are also indefinite as the amino acid position(s) can be filled an indeterminate number of alternative embodiments, therein rendering the claims indefinite. In support of this position, attention is directed to page 36, penultimate paragraph, of the specification, which states in part:

Preferred polymerases for use in this invention include mutants or mutated variants of native polymerases where the mutants have one or more amino acids replaced by amino acids amenable to attaching an atomic or molecular tag, which have a detectable property. Exemplary DNA polymerases include, without limitation, HIV1-Reverse Transcriptase using either RNA or DNA templates, DNA pol I from *T. aquaticus* or *E. coli*, Bacteriophage T4 DNA pol, T7 DNA pol or the like. Exemplary RNA polymerases include, without limitation, T7 RNA polymerase or the like.

Given that the expression “*Taq* polymerase” is to include not only wild type polymerase but “mutants or mutated variants of native polymerases,” it is less than clear as to just what these positions are to correspond to, or the value of the amino acid at any one, much less all of the cited positions.

10. Claims 52, 66, 73, 83, and 94 are again rejected as being indefinite with respect to what constitutes the metes and bounds of "SEQUENASE." As noted in the prior Office action, SEQUENASE is a registered trademark, and as such, the product represented by said trademark is subject to change without public notice. While applicant has amended to the claims so to capitalize the trademark, the claims also need to reflect the generic terminology of the product at the time of the invention.

11. The term "close proximity" in claims 18, 55, 69, 77, 87, and 98 is a relative term that renders the claims indefinite. The term "close proximity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

### ***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 10, 16-19, 50-56, 64-74, 76-92, 94-100, 102-106, and 108-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,982,146 B1 (Schneider et al.) in view of US Patent 6,306,607 B2 (Williams) and US Patent 7,037,687 B2 (Williams et al.).

16. It is noted that while Schneider et al., was published 03 January 2006, it claims benefit of priority to provisional application 60/151,580, filed 30 August 1999. In comparison, the instant application claims benefit of priority to provisional application filed 07 July 2000. Accordingly, Schneider et al., qualifies as 102(e)-type art.

17. Schneider et al., disclose methods, and related compositions, for conducting sequencing reactions. As seen at column 5, the polymerase and nucleotides are both labeled, and that can serve as either a donor or acceptor of a signal, which can be fluorophores.

18. Schneider et al., column 9, teach explicitly of the application of fluorescence resonance energy transfer (FRET).

19. Schneider et al., column 10, teaches, "[o]ne of ordinary skill in the art can easily determine...which fluorophores will make suitable donor-acceptor FRET pairs.

20. Schneider et al., column 13, disclose a plethora of polymerizing agents, which include DNA polymerase I, Taq polymerase, reverse transcriptase, and RNA polymerase.
21. Schneider et al., column 25, teach that the fluorophore can be linked directly or indirectly to the nucleotide.
22. Schneider et al., column 9, teach that the donor and acceptor fluorophores need to be within 10 to 100 Angstroms of one another for fluorescence resonance energy transfer to take place. Such a showing is considered to meet the limitation of being within "close proximity" (claims 18, 55, 69, 77, 87, and 98) as well as meet the limitation of 10, 15, or 25 Angstroms-limitations of claims 80, 81, 105, 106
23. Schneider et al., column 24, first full paragraph, teach that the linkage which couples the fluorophore to the nucleotide can be designed such tat it is cleaved, thereby releasing the fluorophore, prior to the incorporation of the next nucleotide.
24. While Schneider et al. disclose numerous polymerases, they do not teach specifically if the polymerases lack exonuclease activity. Additionally, Schneider et al., do not teach that the fluorescent label is released from the nucleotide by action of the polymerase (i.e., cleavage of the terminal phosphates).
25. Williams disclosed methods and related kits for detecting incorporation of a nucleotide by a polymerase where the nucleotide comprises a label attached to the terminal phosphate, and that the terminal phosphate is cleaved by action of the polymerase, thereby releasing a member of a FRET pair into solution.
26. Williams et al., column 4, teach that their method utilizes polymerases that are deficient in exonuclease activity.



27. Williams et al., column 7, disclose polymerases that are useful in such a procedure. As seen therein, one such polymerizing agent is *Taq* polymerase as well as T7 DNA polymerase, Klenow polymerase, reverse transcriptase, etc.
28. Williams et al., column 12, bridging to column 13, disclose using fluorescently-labeled nucleotides, and their being incorporated by the aforementioned polymerases.
29. Williams et al., column 7, disclose compositions which are used to carry out various reactions. Said compositions are described as comprising the above identified nucleotides and polymerases.
30. Neither Schneider et al., nor Williams et al., have been found to disclose using nucleotide where the fluorescent label is attached to a terminal phosphate.
31. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Schneider et al., by using nucleotides that comprise a member of a FRET pair located on a terminal phosphate a such would allow for the ready detection of changes in signal frequency, signal intensity, and/or duration of signal as each nucleotide is incorporated into a nascent strand. It would have also been obvious to said ordinary artisan to have modified the composition of Schneider et al., by incorporating into the composition polymerases that lack exonuclease activity as such would have resulted in greater efficiency and reproducibility of the assay.
32. In view of the detailed teachings, said ordinary artisan would have been amply motivated and would have also had a most reasonable expectation of success. For the above reasons, and in the absence of convincing evidence to the contrary, claims 10, 16-19, 50-56, 64-74, 76-92, 94-100, 102-106, and 108-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over US

Patent 6,982,146 B1 (Schneider et al.) in view of US Patent 6,306,607 B2 (Williams) and US Patent 7,037,687 B2 (Williams et al.).

***Conclusion***

33. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

34. A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

36. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

37. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/  
Primary Examiner, Art Unit 1634